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Lithium concentrations in plasma of lithium-treated psychiatric patients in the Netherlands: commentary on Cusin et al.

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Abstract

Seasonal variations in 68 psychiatric patients receiving prophylactic lithium treatment in the Netherlands between 1974 and 1994 were analyzed and compared with findings from Italy. Although lithium doses remained stable, there was a significant change in plasma levels of lithium, with values in spring and summer tending to exceed those in autumn and winter. These findings are similar to those reported in Italy, although the maximal seasonal change was approximately 5% in the Netherlands compared with approximately 10% in Italy. The difference could reflect the hotter summer climate in Italy, associated with increased perspiration. Future studies should measure perspiration levels directly. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Seasonality; Major depressive disorder; Bipolar disorder; Mood ratings; Cross-national comparison

1. Introduction

The study by Cusin et al. (2002) on seasonal variation in lithium plasma levels of lithium-treated psychiatric patients in Italy has renewed our interest in a similar analysis that was performed in the Netherlands and has not been published. The similarities and dissimilarities of the two studies will be described and discussed to substantiate and specify the conclusions reached by Cusin et al.

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2. Methods

A total of 68 psychiatric patients (41 females, 27 males) receiving prophylactic lithium treatment who had been recorded between 3 and 20 years each (mean \pm S.D. = 10.0 ± 4.6 years) in the years between 1974 and 1994 were included in the analysis. Clinical diagnoses were bipolar disorder ($n=53$), major depression, recurrent (unipolar depression; $n=12$), and schizoaffective disorder ($n=3$). Lithium concentrations were determined at an average rate of once per 6 weeks. Simultaneously, the prescribed doses of lithium were recorded as well as subjective mood ratings. The mood ratings were performed as follows: If the patient had no complaints about the prior 6-week

Table 1
Lithium doses and plasma levels per season, means and standard deviations

Season	Winter	Spring	Summer	Autumn
Lithium dose (mg)	1136 ± 288	1136 ± 295	1132 ± 291	1133 ± 299
Lithium plasma level (mmol/l)	0.718 ± 0.105	0.740 ± 0.125	0.744 ± 0.116	0.706 ± 0.112

interval, mood was rated 5. If the patient had felt depressed, mood was rated 4. If he or she consulted a physician because of depressive symptoms, mood was rated 3; if the patient was hospitalized for depression, mood was rated 2. Similarly, complaints of mania or hypomania were rated from 6 to 8, depending on the necessity of visiting a physician or of hospitalization.

3. Results

For each subject, the average lithium dose and lithium plasma levels were determined per season, with March 21, June 21, September 21, and December 21 being taken to mark the transitions of the seasons. Table 1 presents the results.

A repeated measures analysis of variance (ANOVA) for lithium dose across the seasons did not reveal significant change ($F=0.244$, $P=0.866$). In contrast, a repeated measures ANOVA for lithium plasma level across the seasons did show a significant change ($F=7.217$, $P=0.000$). Post hoc comparisons revealed that the spring and summer values exceeded autumn and winter values in each of the possible combinations of comparisons. Differences between spring and summer and between autumn and winter were not significant. Lithium plasma levels and mood ratings did not correlate significantly in 56/68 patients (Spearman rank correlation coefficient >0.05). In one patient, however, a significant positive correlation was observed; in 11 patients, a significant negative correlation was found, which in the latter group explained 9.4% of the variation. In most cases, the negative correlation reflected feelings of depres-

sion (score 4) that coincided with somewhat higher lithium levels in plasma.

4. Conclusion

In spite of a constant level of prescribed lithium dose, lithium-treated psychiatric patients in the Netherlands demonstrate an annual modulation of plasma levels of lithium, peaking in spring and summer. Maximal seasonal change is approximately 5% in the Netherlands, as compared with approximately 10% in Italy. This difference is consistent with the suggestion by Cusin et al. that the increase in summer may be due to increased perspiration: summers are not so hot in the Netherlands as in Italy. Actual perspiration levels should be measured to substantiate the relationship and to test whether the differences in spring between the study by Cusin et al. and our own study can be explained by differences in perspiration in spring between Italy and the Netherlands. In our study, the relationships between lithium blood levels and mood were not significant in the majority of patients. Moreover, levels of mania or hypomania were not significantly increased in autumn. Thus, the change in lithium concentrations across the seasons does not appear to have influenced the rate of manic or hypomanic symptoms. One aspect of these studies that is of clinical importance, however, is that high plasma levels in early spring may, without change in prescribed dose, develop into toxic levels in summer.

References

- Cusin, C., Serretti, A., Mandelli, L., Lucca, A., Smeraldi, E., 2002. Seasonal variations of lithium plasma levels. *Psychiatry Research* 110, 35–41.